ASBMT American Society for Blood and Marrow Transplantation

Combined Submyeloablative and Myeloablative Dose Intense Melphalan Results in Satisfactory Responses with Acceptable Toxicity in Patients with Multiple Myeloma

Nicolas Novitzky,[1,2] Jaqueline Thomson,[1] Valda Thomas,[2] Cecile du Toit,[1,2] Zainab Mohamed,[3] Andrew McDonald[1,2]

We studied in patients with multiple myeloma (MM) the efficacy, cost-effectiveness, and toxicity of a strategy of submyeloablative doses of Mel and stem cell support in the ambulatory setting, followed by a standard myeloablative dose transplant. Patients with recently diagnosed symptomatic MM received dexamethazone to induce clinical response. Cytokine mobilized peripheral blood progenitor cells (PBPC) were split into 2 aliquots and cryopreserved. Patients then received Mel 100 mg/m^2 (Mel100) and infusion of the first PBPC aliquot in an ambulatory facility. Individuals received standard neutropenia prophylaxis and no growth factor support, but were seen regularly at the clinic until recovery. The cost of this step was calculated in a cohort of 23 patients where information for the expenditure was available. Six months later patients were conditioned in the hospital with Mel 200 mg/m^2 (Mel 200) followed by nfusion of the second aliquot. This study tested the cost, effectiveness, and the toxicity of out-patient-based transplantation, as well as the rate of response (complete remission [CR], very good partial remission [VGPR], partial remission [PR], and stable disease [SD]) and overall survival (OS) of this strategy. Twenty-six female and 16 male patients, with a median age of 53 years (range: 33-68 years) and median Salmon & Durie clinical disease stage III (range: II-III) were studied. The paraprotein was IgA in 17%, IgG in 52%, and light chains in 26%. The median harvested CD34$^+$ $\times$ 10^6 cells/kg was 12.03 (2.25-55.4). The median interval between the 2 transplant procedures was 239 (105-376) days. The median Karnofsky presentation score was 40%, but improved to 80% after the Mel 100 and was 90% following Mel 200. Subsequent to MEL 100 response was complete (CR) in 7 and it was VGPR in 9. Mel 100 grade 3-4 toxicity was mainly hematologic, but 15 (36%) required hospital admission for a median of 5 days. The median cost of MEL100 and corresponding supportive therapy was U.S. $2,142.35. In addition, the total median cost of those who needed admission to hospital was U.S. $6,042.78. Thus, pooling costs from patients who needed or did not need admissions the average cost of this strategy was U.S. $3,546.50 per patient. Among Mel 200 patients, except for hematologic toxicity, no patient had greater than grade 2 side effects. On completion of the program, 20 (48%) patients achieved CR, a further 14 (33%) had VGPR, whereas 6 had PR. At a median follow-up of 659 days there were 8 deaths, 1 (2%) was related to the treatment procedures and 6 from disease progression; thus, the 1000 days OS was 73%. Significant adverse factors included older age, lower presentation Hb, and lower Karnofsky %. Non-parametric testing confirmed that good performance scores and VGPR or CR were associated with more favorable outcome. Importantly, these satisfactory results were obtained in the absence of the new biologic cell modifiers. Mel 100 was well tolerated in the outpatient setting and the overall strategy seems to be effective in inducing durable responses with acceptable toxicity.

Biol Blood Marrow Transplant 16: 1402-1410 (2010) © 2010 American Society for Blood and Marrow Transplantation

KEY WORDS: Multiple myeloma, Autologous stem cell transplanation, Submyeloablative conditioning

From [1]The University of Cape Town Leukaemia Centre and the Division of Haematology, Department of Medicine; [2]Clinical Laboratory Sciences, Faculty of Health Sciences, University of Cape Town; and [3]Department of Radiation Medicine, Groote Schuur Hospital, Observatory 7925, Cape Town, South Africa.

Financial disclosure: See Acknowledgments on page 1409.

Correspondence and reprint requests: Nicolas Novitzky, Dip Med, FCP(SA), Ph.D(UCT), Department of Haematology, University of Cape Town Medical School, Anzio Road, Observatory, 7925, Western Cape, South Africa (e-mail: nicolas.novitzky@uct.ac.za).

Received June 10, 2009; accepted April 2, 2010

1083-8791/$36.00
doi:10.1016/j.bbmt.2010.04.002

INTRODUCTION

Despite substantial progress in our understanding of the biology of multiple myeloma (MM) and the availability of new treatment modalities, it still remains essentially an incurable disease. Over the last 20 years, a number of strategies have been developed that have resulted in significant improvement in the control of the malignancy, and even leading to complete remissions in a significant fraction of patients. These strategies include the introduction of dose-escalated melphalan (Mel) with autologous stem cell transplantation (SCT) [1-4], and more recently, disease modulation with biologic cell modifiers such as thalidomide [5], lenalidamide [6], and bortezomib [7], alone or in combination with corticosteroids and cytotoxic agents [8]. Thus, with these emerging options, the optimal management of symptomatic patients still remains to be defined; however, because myeloma still constitutes an incurable disease, both improvement in the length and the quality of life must be equivalent goals. Yet, for those who do not have contraindications, autologous SCT remains the gold standard in the management of this condition. Following high-dose therapy there is rapid control of the malignancy, and around 50% of patients may show no morphologic or chemical evidence of the disease, a state that has been associated with improvement in survival [3,8,9]. As for the older population, this procedure is still associated with substantial morbidity. Palumbo and colleagues [10] tested lower doses of dose-intense Mel (submyeloablative; 100 mg/m^2) and also observed substantial responses with lower toxicities [10]. In addition, a number of investigators have shown that long-term survival was associated with good response to this therapy, and that for certain patients, 2 transplants, in tandem, increased the rates of such favorable responses [11-14].

We, therefore, describe a stepwise therapeutic approach where patients with symptomatic myeloma were offered induction therapy with dexamethasone, followed by harvesting of sufficient stem cells for 2 autologous SCTs. The first conditioning was with intermediate dose melphalan (melphalan 100 mg/m^2 [Mel 100]), followed by the infusion of the first aliquot of autologous stem cells. Patients were fully managed in the ambulatory setting. We calculated the costs of this intervention to determine cost effectiveness compared to current modalities. Once individuals recovered from the initial therapy, approximately 6 months later, they received the second full dose conditioning (melphalan 200 mg/m^2 [Mel 200]) in a high-care ward. We show here that this strategy was associated with good disease control, was well tolerated, and has resulted in encouraging long-term outcome.

PATIENTS AND METHODS

Definitions and Diagnostic Criteria

Between 2003 and 2008, patients with Salmon & Durie stage II or III [15] symptomatic MM, aged up to 65 years and Karnovsky performance status >30% were eligible for the study. Consent for therapy was obtained according to the directives of the University of Cape Town. Diagnosis of MM was made in line with the criteria of the Chronic Leukemia-Myeloma Task force [16]. Entry conditions were symptomatic disease in patients who had no contraindications for intensive chemotherapy with high-dose Mel, as well as acceptable vascular access to undergo apheresis. Exclusion factors were cardiac ejection fraction of <45%, vital pulmonary capacity of <45% of the predicted value, estimated creatinine clearance of <30 mL/min, active hepatitis B or C virus infection or HIV reactivity, as well as uncontrolled epithelial cancer or psychiatric disease. The primary objective was to determine the efficacy and toxicity of ambulatory conditioning with submyeloablative dose-intensified Mel followed by SCT. The secondary end points were to quantitate the rate of complete remission (CR), disease free survival (DFS), and overall survival (OS) for this strategy of tandem transplantation. We also attempted to calculate the costs of this outpatient strategy in the South African setting. Study population included newly diagnosed patients with MM who were treated with a steroid-based induction.

Supportive Measures

Groote Schuur Hospital is a state health institution that serves mainly patients without medical insurance. Patients are often in need of financial assistance to be able to attend hospital visits and have limited family support. To participate in the current program patients underwent a psychosocial evaluation to determine their ability to care for themselves, their understanding of the complexities of this protocol, to make certain of their compliance, as well as to ensure that they had adequate family support. Individuals were required to have a care giver readily available, to test their body temperatures every 8 hours, and have easy access to the hospital. For all patients receiving initial therapy, usual neutropenia prophylaxis applied. Following submyeloablative conditioning and graft infusion, patients were requested to attend the clinic 3 times a week to detect possible complications of leukopenia and for evaluation of nausea and oropharyngeal mucosal damage (mucositis) by chemotherapy. Uncontrolled nausea and vomiting despite serotonin inhibitor antiemetics, pyrexia higher than 38°C, or clinical manifestations of malnutrition/dehydration from mucositis were all indications for prompt admission to the hospital.

Treatment of MM

Recently diagnosed patients with symptomatic MM were treated with dexamethasone 40 mg daily on days 1-4, 8-11, and 18-21, every 28 days for 4 cycles. After the completion of the fourth series of dexamethasone and of the corresponding treatment response evaluation, regardless of initial outcome, patients underwent stem cell mobilization as an ambulatory procedure. Mobilization chemotherapy consisted of etoposide 1 g/m^2 on each of 2 consecutive days. Patients were taught to inject and received filgrastim (Neupogen, Roche Pharmaceuticals, Indianapolis, IN, USA) 300 μg subcutaneously twice daily for 7-10 days, starting on day 5. On day 14 following mobilization chemotherapy, peripheral blood progenitor cells (PBPCs) were enumerated according to ISHAGE recommendations [17] and apheresis was commenced once CD34$^+$ cell count exceeded 5×10^6/mL. Apheresis was undertaken with continuous cell separator (Cobe Spectra, NJ, USA) and enough progenitor cells for 2 procedures were collected. The minimum target CD34$^+$ was 2×10^6/kg, per graft.

After premedication with allopurinol 300 mg, parenteral prehydration and antiemetics, patients had a single intravenous infusion of Mel 100 in the clinic. Twenty-four hours later cryopreserved PBPC were thawed in a 37°C water bath and the first aliquot of stem cells was rapidly transfused in the outpatient section. Oral neutropenia prophylaxis consisted of ofloxacin 200 mg twice a day and daily fluconazole (400 mg); antiemetic agents were continued for 72 hours or while patient remained symptomatic. Individuals receiving the first graft were then requested to attend the clinic on alternate days until recovery of neutropenia. Hematopoietic growth factors were not offered. Approximately 6 months following the initial transplant, patients with MM were admitted to the protected environment unit at Groote Schuur Hospital and a siliconized double lumen indwelling catheter [18] was inserted percutaneously into the internal jugular vein. Patients were prescribed similar protective measures and neutropenia prophylaxis as for the initial conditioning chemotherapy. For the second transplant, patients received Mel 100 mg/m^2 on each of 2 consecutive days (total dose 200 mg/m$^{2;}$; MEL 200), as a 30-minute infusion.

Evaluation of Response

Evaluation of response required review of the bone marrow (BM) plasmacytosis, protein electrophoresis with immunofixation, as well as determinations of β2 microglobulin and of serum chemistry, which were performed at 8-12 weeks after the first and second autologous transplants [19]. Part of this evaluation included determination of the changes in the performance status using Karnovsky scale. Response type was defined following the IMF recommendations [17,20]. CR required absence of plasmacytosis from the BM and of the serum praprotein on immunofixation. Disease progression implied at least a 25% increase in tumor mass, BM plasmacytosis, or any new disease manifestation. Relapse was defined as recurrence of monoclonal protein or BM plasmacytosis or evidence of extramedullary disease in case of CR, very good partial remission (VGPR), or partial response (PR), including any new disease manifestation such as hyper calcemia or new bone lesions. Treatment-related mortality (TRM) included any death within 30 days posttransplantation.

Evaluation of Costs

Most medication in the state hospital in South Africa is procured at State Tender prices, which are substantially lower than those charged to the general public by private pharmaceutical drug suppliers. Biologic agents such as thalidomide or bortezomib are not available at state hospitals, but may be purchased from pharmacies privately, or once approval from insurance companies has been obtained. Patients who have health insurance pay for the cost of the medication at a single exit price (SEP), which is negotiated between the pharmaceutical companies and the Health Department. We retrospectively determined the cost for the induction phase with the Mel 100 program (inclusive of value added tax) by calculating the costs of the reagents to store the stem cells, conditioning, and of supportive drugs applying the SEP for all pharmaceuticals used and added the costs of consultations at the hospital. We calculated the cost of consultations and hospital admission tariffs according to the Department of Health National Reference Price List (www.doh.gov.za/docs/nhrpl-f.html) tariffs charged by medical insurance as well as the cost of blood product support as per Western Province Blood Transfusion Service price list (www.wpbtsmedical.org.za/images/Private09.pdf; year 2010).

Statistical Methods

Standard population statistics were employed to define the patient population. Median cost of outpatient and in hospital therapies for Mel 100 were calculated. Final costs were estimated by adding the expenses generated by hospital admissions of 15 patients to the outpatient expenses. Survival analyses were performed using the product limit estimate of the Kaplan-Meier method. Significance in the difference of survival curves from various groups was compared by the log-rank test. To predict outcome, pretransplant variables analyzed were lactate dehydrogenase (LDH), albumin, BM plasmacytosis, time to second transplant, and response to salvage chemotherapy by nonparametric statistics. Patients were

followed up at the clinic or telephonically. Patients were studied for response TRM, OS, and event-free survival (EFS) according to IMWG criteria. OS was calculated from time of first dose of dexamethasone.

RESULTS

Patients' Demographic and Clinical Data

The characteristics of the patient population at entry are shown in Table 1. All patients had symptomatic disease. On presentation the renal function was abnormal in 10 patients, and it normalized with treatment in all except 1. The median Karnofsky score at diagnosis was 40% but improved to 80% after the Mel 100 and was 90% following Mel 200 (Figure 1). As patients progressed through the treatment sequence, improvement of paraprotein level, BM plasmacytosis, Hb, serum albumin, β2MG, and Karnofsky status can be observed in Figure 1.

Following dexamethasone-based induction, evidence of response (CR + VGPR + PR) was observed in 25 (61%) individuals. In this group, 2 patients achieved CR and another 3 VGPR, whereas 20 were in PR. Disease parameters decreased by less than 50% or remained stable in another 13 individuals; MM progressed in 2 patients. Response data was not available in 2 individuals. Regardless of type of response, all patients proceeded to the transplantation stage.

Stem Cell Transplantation Parameters and Treatment Outcomes

After stem cell mobilization with etoposide, the median harvested $CD34^+$ cells/kg was 12.3 (range: 2.25-55.4; Table 2). The median number of apheresis procedures was 1 (1-3). However, in 1 individual the circulating $CD34^+$ cell number decreased rapidly and PBPC available allowed only 1 transplant, which followed a single Mel 200 conditioning. Thus, sufficient $CD34^+$ cells for the 2 procedures were collected in 40 subjects and it was with a single apheresis in 35 (87.5%) patients. There was no significant difference in the $CD34^+$ cell number infused between the 2 transplants. The median interval between the 2 transplant procedures was 212 (105-376) days, the delay being mainly because of logistic and operational reason (availability of a bed for admission). One patient failed to receive the second graft because of a vascular access catastrophe that led to the patient's death in VGPR. Thus, a total of 41 patients received the first graft and 40 individuals completed the full program. Respectively, the median time to neutrophil and platelet recovery was 14 and 18 days for the first procedure and 13 and 17 days for the second. No maintenance therapy was prescribed until disease recurrence.

Table 1. Clinical and Laboratory Parameters of the Study Population

Parameter	Value
Age, years median (range)	53 (33-68)
Sex distribution, F/M	26/16
Parapotein type, patient No. (%)	
IgA	7 (17)
IgG	22 (52)
Light chain	11 (26)
Non secretor	2 (10)
β2 microglobulin mmol/L median, (range)	2.4 (1.4-8.1)
Abnormal No. (%)	12 (29)
Salmon & Durie clinical stage, median (range)	III (II-III)
ISS median, range	1 (0-2)

ISS indicates International Scoring System;[19].

All patients showed some improvement of MM after stem cell mobilization with etoposide (and filgrastim), conditioning with Mel 100 and infusion of the first graft. CR was now observed in 7 patients (5 additional), whereas 9 (6 additional) had achieved VGPR (38% CR + VGPR). One patient in CR died during the insertion of Hickman line before the Mel 200 treatment. Two individuals who had progressed after dexamethasone now achieved PR and VGPR. After the second graft, a stringent evaluation showed that 20 (48%) patients achieved CR, a total of 14 (33%) had achieved VGPR, whereas another 6 were in PR. Disease progressed in 1 subject. Compared to the outcome of the lower intensity schedule, Mel 200 improved the response of most initially responsive patients and resulted in 81% achieving CR or VGPR. One patient who had responded to Mel 100 progressed rapidly after Mel 200. At relapse patients were treated with various alkylators, biologicals, or anthracycline-based combinations. One patient died following motor vehicle accident. At the time of the analysis, 5 had progressed but had stable disease on further therapies and 6 patients had died of progressive multiple myeloma. At 8-12 weeks following Mel 200, plasmacytosis >10% was detected in 5% (n = 40; Figure 1A).

At a median follow-up of 648 days, there were 8 deaths: 1 (2%) was directly related to the treatment procedures, 1 from a motor vehicle accident, and 6 from disease progression (Table 2). Median survival has not been reached. For the complete cohort, the 1000-day survival is 73% (Figure 2A). Figure 2 shows that there was significant difference in survival between the 3 response groups, with CR or VGPR resulting in better outcome compared to the PR group (Figure 2B; $P = .01$). On multivariate analysis, significant adverse factors for survival included lower (than median) Hb on presentation ($P < .01$), lower Karnofsky % ($P < .01$), and older age ($P = .04$).

Toxicity (Table 3)

Toxicity of dexamethasone was predictable, of mild nature, and was well controlled with standard

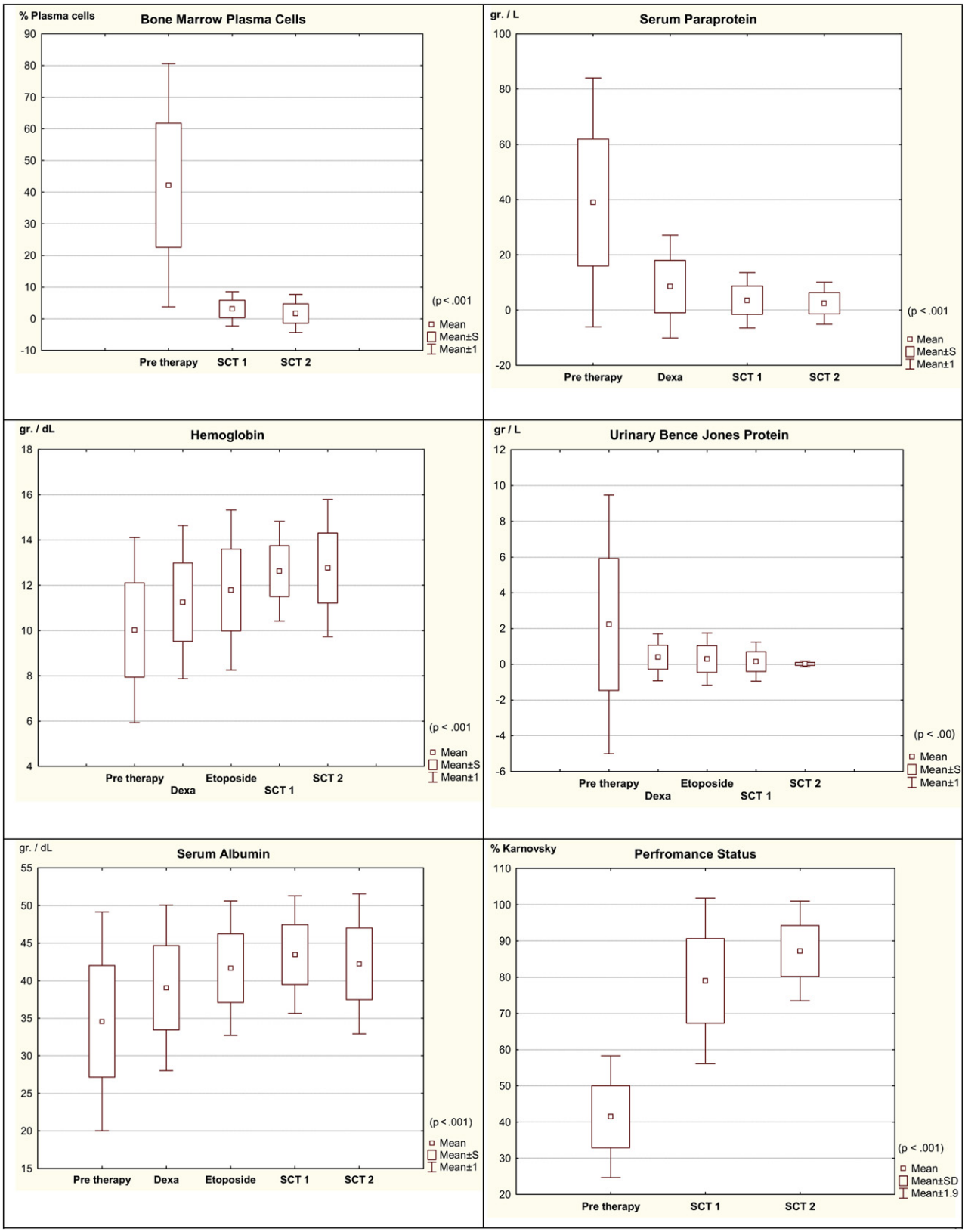

Figure 1. Graphical representation of the laboratory parameters and of Karnofsky scores at the different stages of the described therapeutic strategy. All the values are significantly different from the presentation parameters. (Dexa: dexamethasone; SCT 1 and 2: stem cell transplant 1 and 2).

Table 2. Autologous Stem Cell Transplantation in Tandem: Cause of Death and Overall Survival

Treatment Outcome (No. 42)	
All deaths:	8
TRM	1
Other	1
Progression of myeloma	6
Follow up, median days	648 (111-1824)
% surviving	75%
% in response	41%

TRM indicates treatment-related mortality; OS, overall survival.

supportive measures. Mobilization of $CD34^+$ cells with etoposide at 2 g/m^2 gave mainly hematologic and gastrointestinal toxicities. All patients developed severe (grade 3-4) neutropenia; 5 patients were admitted with neutropenic fever and all responded to antibiotics. Grade 2 mucositis occurred in 18 individuals, but none showed grade 3 or 4 toxicities. All underwent stem cell harvest without delays.

The toxicity of Mel 100 was manageable in the outpatient setting (Table 3). All patient developed grade 4 hematologic toxicities and 10 individuals required transfusion of red cells (median 2 units) and, in 6 cases, of platelets (median 1 single donor unit). Fifteen patients required admission to hospital, mainly for neutropenic fever, for a median of 5 days. One patient in VGPR and normal blood parameters died of bleeding during the insertion of a Hickman line before the second transplant. Mel 200 was associated with the usual side effects, but except for hematologic toxicity, no patient had greater than grade 2 side effects. There was no mortality after conditioning with Mel 100 and Mel 200.

Cost of Therapy

The expenditure of Mel 100 induction therapy received by 23 individuals where detailed drug usage was available was calculated. The median cost of Mel 100 and corresponding supportive therapy was R 16,281.80 (range: 15,441.14-3278.60) or U.S. $2,142.35 (1Rand: 7.60 U.S. $). In addition, the total median cost of those who needed admission to hospital (in a private facility) for the typical complications was R 45,925.10 (U.S. $6.042,28). Thus, because 36% required admission for complications of dose intense Mel 100 for a median of 5 days, the average cost until recovery of this strategy pooled from 10 patients who needed or did not need admissions was R 26,953.40 (U.S. $3,546.50).

DISCUSSION

The combination of oral Mel and prednisone has been the mainstay in the treatment for patients with MM for 4 decades. Other cytotoxic combinations such as infusional vincristine, adriamycin, and high-dose dexamethasone (VAD) [21], etc., have also been explored but in a meta-analysis, these more complex schedules did not significantly improve survival [22]. Moreover, dexamethasone appears to be the most active ingredient in the VAD combination leading to similar outcomes as the substantially more complex and toxic 3-drug combination. Nevertheless, most patients will experience disease recurrence and then further management remains unsatisfactory. For this reason, in a prospective randomized study, the Intergroup Francophone pour l'etude du Myelome (IFM) showed that in myeloablative doses Mel followed by autologous stem cell infusions was associated with significantly better responses and more extended survival than standard dose salvage therapy [3]. Thereafter, these and other investigators suggested that 2 autologous transplants in tandem led to superior DFS and OS,

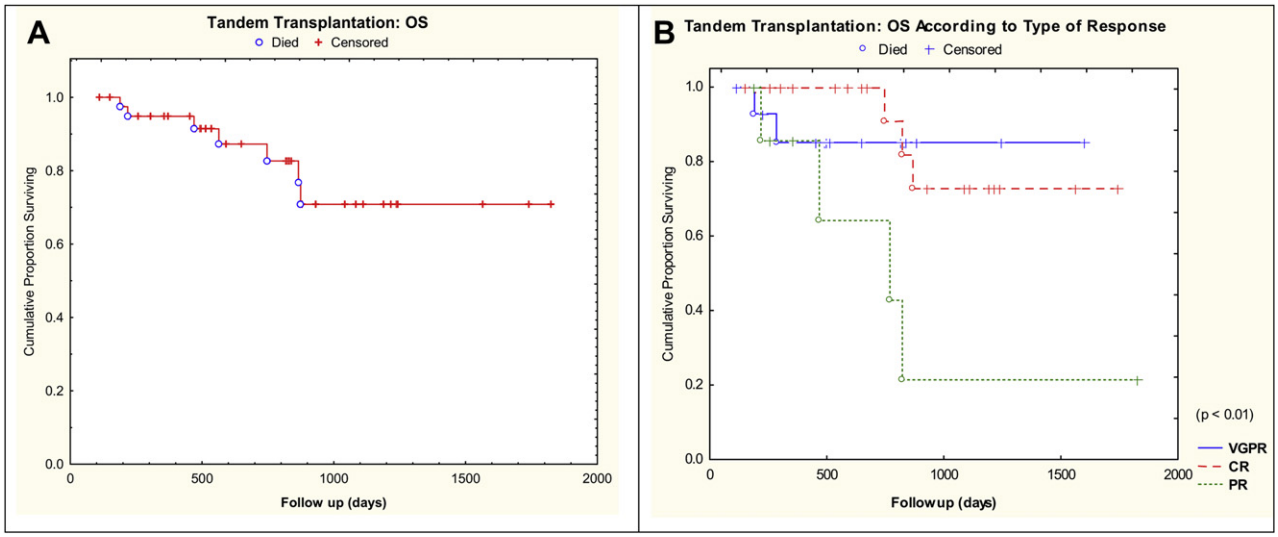

Figure 2. OS of the study population. (A) Shows the overall outcome. (B) Shows the outcome according to type of response to the therapeutic strategy. Patients who failed to achieve at least VGPR had significantly worse outcome.

Table 3. Toxicity Scores of the Mel 100 and Mel 200 Conditioning Programs

	Mel 100 (n = 41)	Mel 200 (n = 40)
Mucositis (WHO) patient No.		
I	7	6
II	12	25
III-IV	0	9
Fever >38 °C	15	38
Number of hospital admissions	15	40
Days in hospital, median (range)	5 (4-9)	17 (14-28)
Blood component support median, (range)		
Platelets	1 (0-6)	4 (1-11)
Red cells	2 (0-2)	3 (0-7)
Time to engraftment		
Days of granulocytes <0 .5 $\times$ 10^9/L	6 (4-7)	7 (3-16)
Days of platelets <50 $\times$ 10^9/L	2 (2-4)	13 (4-19)

particularly for patients who failed to achieve at least VGPR after the first procedure [11,12,14,23]. This observation was not universal, however [24].

Recently, a number of biologic cell modifiers (thalidomide, bortezomib, or lenalidomide) have been shown to improve disease control in patients with recurrent MM or in the upfront setting [25-27]. Nonetheless, intensified dose melphalan still remains the gold standard in the treatment of younger patients, although its place in the therapeutic sequence in the context of these newer agents is currently being debated. However, state hospitals in South Africa do not receive funding for these new agents. Consequently, we prospectively studied patients with symptomatic myeloma to determine the effectiveness of this strategy and establish their outcome after the combination of Mel 100 and Mel 200 in tandem, each supported by infusion of autologous stem cells. As our induction agent we chose dexamethazone, which, regardless of response, was followed by stem cell mobilization, stem cell harvest, and then the ambulatory transplant procedure.

For the mobilization of stem cells, we elected to use high-dose etoposide as in previous studies it had been particularly effective in "poor mobilizers" compared to cyclophosphamide [28,29]. This was of significant relevance, as because of cost constraints, we wanted to harvest the required progenitor cells for the 2 transplants with 1 apheresis procedure only. Additionally, etoposide has potent cytotoxic effects against malignant plasma cells either in vitro or in clinical studies and has been included in various chemotherapeutic schedules [13]. Indeed, sequential monitoring of some of the disease parameters showed that after infusion of etoposide, even before the first treatment of dose intensified Mel, a significant reduction in the serum paraprotein level was observed, with consequent improvement of the serum albumin and blood hemoglobin levels (data not shown). This may be one of the reasons that after the Mel 100 evaluation the complete response rate and VGPR were superior to another study [10,30]. Other reasons could be the younger age of our population and possible patient selection bias.

Including a vascular access complication (not directly related to the study protocol), the overall procedure mortality was 2%, which is not different from that of therapy with VAD like combinations or the experience in other high dose programs. However, individuals entering such programs must be carefully evaluated and informed of the possible toxicities associated with dose intense chemotherapy; 36% of patients undergoing submyeloablative conditioning required admission to hospital for the treatment of intractable nausea, mucositis or neutropenic fever (Table 3). Provided patients are compliant and closely monitored, this strategy is feasible in the outpatient setting; it can considerably reduce the number of patients who may need to be admitted to hospital and thus reduce the costs of this program.

Moreover, the outcome after Mel 200 and SCT is closely related to performance status, which was poor in most patients presenting to our clinic (median presentation Karnofsky score of 40%; Figure 1). This, together with the substantial pressure on our high care beds, led us to prescribe the first Mel 100 [10] in the ambulatory setting as a treatment induction step. At this lower dose nausea and vomiting as well as "mucositis" were less problematic, with minimal treatment related toxicities and no direct mortality (Figure 1). Of interest, we noted that responses to Mel 100 appeared similar to those described with the new biologic agents. To determine the cost effectiveness of this strategy, we calculated the costs for the conditioning with MEL100, together with outpatient therapy with antiemetic agents, neutropenia prophylaxis, and 3 weekly visits to the clinic with the corresponding laboratory monitoring tests until recovery. We determined that the median outpatient expenditure from 23 patients was U.S. $2142.35 (range: 15,441.14-3278.60). The median admission costs from 11 patients was U.S. $6042.78 (range: 3900.98-9,786.34), leading to an overall estimated total expenditure of U.S. $3546.50, if the average of 10 patients was considered. This would compare favorably with the cost of induction therapy with thalidomide (Thalomid; Key Oncologics, South Africa; R: 10407.12 or U.S. $1387.61per 28 day course at a dose of 200 mg/day) or bortezomib (Velcade, Janssen-Ceilag Pharmaceuticals, Johannesburg; R 55,346.92 (U.S. $7379.59) for 3 week cycle), even without considering other drug additions, the costs of screening visits and corresponding monitoring laboratory investigations. Thus, the cost for the collection of the additional grafts and outpatient transplantation after the Mel 100 procedure, inclusive of 36% of possible admissions to hospital, was lower than the single exit price of 3 months of thalidomide or 1 cycle of boterzomib. Approximately 4-6 cycles of each strategy

are recommended. Mel 100 was well tolerated with no grade IV (except hematologic) toxicities reported.

On final evaluation at the end of therapy, with this strategy complete remission occurred in 48% of all patients, whereas another 33% achieved VGPR and only 2% had progressive disease. Patients achieving this favorable response status had a significantly better survival than those not meeting VGPR criteria (Figure 2B). These data appear similar to the results of a larger experience of "Total Therapy 1" by an Italian group [24]. Nonparametric statistics indicated that that better median presentation PS score higher median Hb and achieving CR or VGPR were associated with longer survival.

There are substantial difficulties in comparing outcomes of trials in myeloma because of individual patient and disease heterogeneity. However, considering the toxicity of some of the novel agents, the results presented would suggest that this strategy seem to provide reasonable compromise between treatment affordability, effectiveness, and toxicity of the procedure. For communities where the modern biologic cell modifiers are not readily available, this approach is a cost-effective option, particularly for those who are responsive to initial therapy, as response status pre Mel 200 seems to be important for the post transplantation outcome [31]. In responders, Mel 200 led to a substantial improvement in the outcomes compared to Mel 100, and thus must remain as the preferred intensification schedule. Last, if the novel agents are accessible, their incorporation as a maintenance program may provide greater long-term effectiveness, as previous exposure has been associated with reduced response, at least in the relapse setting [13]. Currently there are prospective trials attempting to define the optimal therapeutic place for these agents and of the intensified Mel schedules. The outcome of these studies is eagerly awaited.

ACKNOWLEDGMENTS

We acknowledge the contributions by the staff at the Cytapheresis Unit and the Protected Environment section. We thank Mrs. C. Fredericks for the editorial assistance and all the participating patients.

Financial disclosure: The authors have nothing to disclose.

REFERENCES

1. McElwain TJ, Powles RL. High-dose intravenous melphalan for plasma-cell leukaemia and myeloma. *Lancet*. 1983;2:822-824.
2. Attal M, Huguet F, Schlaifer D, et al. Intensive combined therapy for previously untreated aggressive myeloma. *Blood*. 1992;79: 1130-1136.
3. Attal M, Harousseau JL, Stoppa AM, et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. Intergroupe Francais du Myelome. *N Engl J Med*. 1996;335:91-97.
4. Child JA, Morgan GJ, Davies FE, et al. High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. *N Engl J Med*. 2003;348:1875-1883.
5. Palumbo A, Facon T, Sonneveld P, et al. Thalidomide for treatment of multiple myeloma: 10 years later. *Blood*. 2008;111: 3968-3977.
6. Armoiry X, Aulagner G, Facon T. Lenalidomide in the treatment of multiple myeloma: a review. *J Clin Pharm Therapeut*. 2008;33:219-226.
7. San Miguel J, Bladé J, Boccadoro M, et al. A practical update on the use of bortezomib in the management of multiple myeloma. *Oncologist*. 2006;11:51-61.
8. Ludwig H, Strasser-Weippl K, Schreder M, Zojer N. Advances in the treatment of hematological malignancies: current treatment approaches in multiple myeloma. *Ann Oncol*. 2007; 18(Suppl 9):ix64-ix70.
9. Barlogie B, Zangari M, Bolejack V, et al. Superior 12-year survival after at least 4-year continuous remission with tandem transplantations for multiple myeloma. *Clin Lymphoma Myeloma*. 2006;6:469-474.
10. Palumbo A, Triolo S, Argentino C, et al. Dose intensive melphalan with stem cell support (MEL100) is superior to standard treatment in elderly myeloma patients. *Blood*. 1999;15:1248-1253.
11. Attal M, Harousseau JL, Michaux JL, et al. Single versus double transplant in myeloma: a randomized trial of the Inter Groupe Francophone du Myelome (IFM). *Blood*. 2000;96:557a.
12. Attal M, Harrouseau JL, Facon T, et al. Single vs. double autologous stem cell transplantation. *N Engl J Med*. 2003;349:2495.
13. Barlogie B, Shaughnessy J, Tricot G, et al. Treatment of multiple myeloma. *Blood*. 2004;103:20-32.
14. Hoering A, Vesole D, Desikan R, et al. Long-term outcome results of the first tandem autotransplant trial for multiple myeloma. *Br J Haematol*. 2006;135:158-164.
15. Durie BGM, Salmon SE. A clinical staging system for multiple myeloma: correlation of measured myeloma cell mass with presenting clinical features, response to treatment and survival. *Cancer*. 1975;36:842-854.
16. Barlogie B, Tricot GJ, van Rhee F, National Cancer Institute. II: plasma cell myeloma: proposed guidelines for protocol studies. *Cancer Chemother Rep*. 1973;4:145-158.
17. Sutherland DR, Anderson L, Keeney M, Nayar R, Chin-Yee I. The ISHAGE guidelines for CD34+ cell determination by flow cytometry. *J Hematother*. 1996;5:213-226.
18. Hickman RO, Buckner CD, Clift RA, et al. A modified right atrial catherter for access to the venous system in marrow transplant recipients. *Surg Gynecol Obstet*. 1979;148:871-875.
19. Greipp PR, San Miguel J, Durie BGM, et al. International staging system for multiple myeloma. *J Clin Oncol*. 2005;23: 3412-3420.
20. Durie BGM, Harousseau J-L, Miguel JS, et al. International uniform response criteria for multiple myeloma. *Leukemia*. 2006;20:1467-1473.
21. Alexanian R, Dimopoulos MA, Delasalle K, Barlogie B. Primary dexamethazone treatment. *Blood*. 1992;80:887-890.
22. The Myeloma Trialists' Collaborative Group. Combination chemotherapy versus melphalan plus prednisone as treatment for multiple myeloma: an overview of 6,633 patients from 27 randomized trials. *J Clin Oncol*. 1998;16:3832-3842.
23. Cavo M, Tosi P, Zamagni E, et al. Prospective, randomized study of single compared with double autologous stem-cell transplantation for multiple myeloma: Bologna 96 clinical study. *J Clin Oncol*. 2007;25. 2434–2434.
24. Galli M, Nicolucci A, Valentini M, et al. Feasibility and outcome of tandem stem cell autotransplants in multiple myeloma. *Haematologica*. 2005;90:1643-1649.
25. Rajkumar SV, Hayman S, Gertz MA, et al. Combination therapy with thalidomide and dexamethazone for newly diagnosed myeloma. *J Clin Oncol*. 2002;20:4319-4323.
26. Richardson PG, Barlogie B, Berenson J, et al. A phase II study of bortezomib in relapsed, refractory myeloma. *N Eng J Med*. 2003; 348:2609-2617.

27. Weber DM, Chen C, Niesvizky R, et al. Lenalidomide plus high-dose dexamethasone provides improved survival compared to high-dose dexamethasone alone for relapsed or refractory multiple myeloma: results of a North American phase III study (MM-009). *J Clin Oncol*. 2006;24:427s.
28. Diehl V, Sohngen D, Engert A. Successful peripheral blood stem cell mobilization with etoposide (VP-16) in patients with relapsed or resistant lymphoma who failed cyclophosphamide mobilization. *Bone Marrow Transplant*. 1999;23:1223-1228.
29. Copelan EA, Ceselski SK, Ezzone SA. Mobilization of peripheral-blood progenitor cells with high-dose etoposide and granulocyte colony- stimulating factor in patients with breast cancer, non-Hodgkin's lymphoma, and Hodgkin's disease. *J Clin Oncol*. 1997;15:759-765.
30. Palumbo A, Bringhen S, Petrucci M, et al. Intermediate-dose melphalan improves survival of myeloma patients aged 50 to 70: results of a randomized controlled trial. *Blood*. 2004;104: 3052-3057.
31. van de Velde HJK, Liu X, Chen G, Cakana A, Deraedt W, Bayssas M. Complete response correlates with long-term survival and progression-free survival in high-dose therapy in multiple myeloma. *Haematologica*. 2007;92:1399-1406.